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BRIEF REPORT

No impairment of pulmonary function in children with Henoch-Schonlein purpura after 4-year follow-up

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Abstract Henoch-Schonlein purpura (HSP) is a generalized form of IgA-mediated vasculitis that usually spares pulmonary circulation. Nevertheless, it is conceivable that subclinical changes at the HSP onset may lead to lung impairment in the long term. Therefore, we decided to follow a group of HSP patients for 4 years to monitor changes in pulmonary function. A group of 11 children and adolescents diagnosed with HSP without apparent pulmonary involvement was subjected to pulmonary function tests (PFTs), i.e., spirometry, body plethysmography, and diffusing capacity for CO (DLCO); these tests were repeated after 48 months. No significant impairment was observed in variables of spirometry, body plethysmography, and DLCO expressed as % of predicted values (% predicted) after 4 years. Specifically, no significant change in DLCO, corrected for blood hemoglobin concentration was noted, i.e., 79.3 ± 10.1 vs. 81.6 ± 14.7 % predicted at the beginning and the end of the study, respectively. IgA vasculitis seems to spare pulmonary circulation as we found no impairment in PFTs within the study time frame and a median of almost 6 years from the first episode of the disease.

Keywords Diffusing capacity for CO · Henoch-Schonlein purpura · IgA vasculitis · Pulmonary function tests

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Introduction

Henoch-Schonlein purpura (HSP) is a form of generalized necrotizing vasculitis related to deposition of IgA immune complexes of unknown origin within small vessels or mesangium in glomeruli. It rarely manifests itself as clinically significant pulmonary disease. Nevertheless, the life-threatening diffuse alveolar hemorrhage syndrome has been reported, but it seems to occur mostly in adults [1, 2]. Moreover, some authors reported reduced diffusing capacity for CO (DLCO) during active disease (even in the absence of pulmonary symptoms) which returned to the baseline after clinical recovery, i.e., the resolution of hematuria [3, 4]. Thus, it is conceivable that deposition of immune complexes within pulmonary circulation may lead not only to acute injury and alveolar hemorrhage, but also to chronic subclinical inflammatory injury with subsequent fibrosis and a widening of the alveolar-capillary barrier. This in turn, may cause a subclinical impairment of pulmonary function with the reduction of DLCO as the sensitive method of its assessment [5]. Therefore, we decided to follow up a group of children and adolescents diagnosed with HSP in respect to changes in pulmonary function tests (PFTs).

Study population and methods

This is a prospective study on a group of 15 children and adolescents (five males) with HSP diagnosis. They were recruited from the database of the outpatient clinic at the Teaching Hospital no. 4 of Medical University of Lodz, Lodz, Poland. They and their legal caregivers were informed about the purpose and procedures of the study and consented to participate. The study protocol was approved of by the Ethics Committee of the Medical University of Lodz (RNN/63/10/

KE). Four of them were lost to follow up due to change in their personal data such as address or telephone number; their pulmonary function test did not reveal any impairment at the first visit (data not shown). The clinical data of 11 patients (four males) that completed the study is summarized in Table 1. The diagnosis of HSP was based on the standard diagnostic criteria, i.e., the classic distribution of purpura plus at least one of the following, not mutually exclusive signs and symptoms: renal involvement, i.e., proteinuria or hematuria (seven subjects), arthritis (nine subjects), or abdominal pain (six subjects); due to the classic clinical presentation, there was no need for histopathologic confirmation in any patient [6]. Seven subjects with hematuria were treated with systemic steroids and fulfilled the criteria of severe HSP at the last exacerbation before the first study visit (V1), Table 1. None of the subjects presented with respiratory symptoms, e.g., cough, dyspnea, or hemoptysis during active disease. Nevertheless, as a part of a standard clinical workup, all of them had a chest x-ray that revealed no pulmonary involvement. The study procedures comprised PFTs: a forced spirometry, an assessment of lung volumes by body plethysmography and the helium dilution method, and single breath DLCO (a 10-s holding breath maneuver at TLC, with the correction for serum hemoglobin levels). All test were performed on MasterScreen Body (Jaeger, Hoechberg, Germany) at the beginning of the study (visit 1 -V1) scheduled at least 1 month after the resolution of the last HSP episode and at the end of the study (visit 2 - V2), i.e., 48 months after V1 (median 48, range 43–56 months). Due to the fact that the subjects were recruited from the outpatient clinic database, there was a substantial time span between the first and the last HSP episode before V1. The individual data referring to the number of HSP exacerbations and their timing related to study visits are presented in Table 1. Only three subjects suffered from HSP relapses between study visits: two patients had one and one had three exacerbations. During these exacerbations, no pulmonary signs or symptoms were reported. Therefore, the time span from the last exacerbation at V2 was quite wide: from 1 to 77, with a median of 50 months. The reference values for PFTs were obtained from the regression equations and were based on the reference data for the Polish pediatric population (obtained from The National Institute for Tuberculosis and Lung Diseases, Pediatric Division in Rabka, Poland). There was no dedicated study control group, but the pediatric population for which predicted values of PFTs were obtained served as one.

The comparison between PFTs values at V1 and V2 was done with Statistica 10 software (Tulsa, OK, USA); the data are presented as a median with range or a mean with standard deviation (SD). To compare PFTs variables at V1 and V2, a paired *t* test was applied due to the normal distribution of data and the specific study design; $p < 0.05$ was considered significant.

Results

During the 4 years of the study, as subjects have grown, there was an expected increase in all absolute PFTs values, Table 2. However, when they were related to the reference values (% predicted), most of PFTs variables did not show any

Table 1 Clinical data of study population at visit 1 (V1) and visit 2 (V2)

Patient nr (sex)	Age at V1 [years]	Nr of HSP relapses prior to V1 and (between V1 and V2)	Time from the first and (the last) HSP episode at V1 [months]	Time from the last HSP relapse at V2 [months]	CRP[c] [mg/dL]	ANCA[c]	ASO[c] [IU/dL]
1[b] (F)	9	1 (0)	6 (6)	50	6.04	neg	182
2 (M)	7	1 (0)	6 (6)	50	0.99	neg	146
3[b] (F)	7	1 (0)	30 (30)	73	0.81	neg	265
4[a,b] (F)	17	3 (1)	18 (10)	40	2.03	neg	90
5[b] (M)	6	2 (0)	22 (21)	77	1.29	neg	170
6[b] (F)	14	2 (0)	33 (30)	75	0.37	neg	210
7 (F)	12	1 (0)	2 (2)	50	0.45	neg	140
8 (M)	10	1 (0)	28 (28)	76	0.78	neg	400
9[a,b] (F)	13	5 (1)	102 (28)	21	1.12	neg	110
10 (M)	14	2 (0)	6 (1)	51	0.62	NA	NA
11[a,b] (F)	19	6 (3)	133 (9)	1	0.89	neg	64
median (range)	12 (6, 19)	2 (1, 6)	22 (10) (2, 133)	50 (1, 77)	0.89 (0.37, 1.60)	–	158 (64, 400)

[a] Patients that experienced at least one relapse of HSP between V1 and V2

[b] Patients with hematuria at the last episode of HSP before V1 treated with systemic steroids

[c] Values are given for the last episode of HSP before V1

CRP C-reactive protein, *ANCA* anti-neutrophil cytoplasmic antibodies, *ASO* (anti-streptolysine O), *NA* not available

significant change; instead, a trend toward higher FEV_1 and FVC at V2 appeared. The only exception was VC that rose significantly by mean of 8 %. The mean DLCO was close to 80 % predicted with negligible change between visits.

No significant difference was observed between lung volumes measured by two independent methods, i.e., body plethysmography and He-dilution (-He), i.e., TLC vs. TLC-He, TGV vs. FRC-He and RV vs. RV-He at both study visits, Table 2.

The majority of children (8 out of 11) did not suffer from a HSP relapse between V1 and V2. The group of three with relapse(es) is too small for any statistical analysis but the inspection of the individual data reveal neither any outstanding values nor a trend towards worse PFTs values.

Discussion

Similar results were obtained by Cazzato et al. on a comparable population, but the time of observation was shorter, i.e., ca 2 years with quite wide range from 12 to 43 months [7]. Four years of follow-up and a median of 22 months from the first episode of HSP at V1 is quite a long time; on the other hand, it may not be sufficient to address the hypothesis of the durable small effect injury that may be clinically apparent long after reaching adulthood. Moreover, all available methods of pulmonary functional assessment may not be sensitive enough to reveal subclinical alveolar injury.

Another factor that may have affected sensitivity of the study was a low number of HSP episodes at the baseline (a median of 2) and between visits. It is conceivable that the number of disease flares and the related vascular injury may affect inversely the pulmonary function. Thus, negative results of our study may stem from this relative low number of HSP episodes. On the other hand, the oldest patient in the group with the largest number of relapses did better at V2 than at V1 with respect to almost all PFTs % predicted values (individual data not shown). Nevertheless, our small group is quite representative as the majority of HSP patients experience only one or two relapses in their lifetime.

DLCO was impaired in HSP patients, but only during acute phase; upon clinical recovery, a normalization of DLCO

Table 2 Comparison of pulmonary function tests at visit 1 (V1) and visit 2 (V2)

Parameter (mean ± SD)	V1	V2	V2–V1 (95 % CI)	*p*
FEV1 [l]	2.14 ± 0.71	2.95 ± 0.87	0.80 (0.44–1.16)	0.0006
(% predicted)	(105.7 ± 15.4)	(112.8 ± 19.4)	7.1 (−0.12–14.3)	0.053
FVC [l]	2.35 ± 0.84	3.22 ± 0.90	0.86 (0.48–1.24)	0.0005
(% predicted)	(102.7 ± 15.8)	(107.6 ± 19.0)	4.9 (−0.5–10.4)	0.072
VC [l]	2.36 ± 0.87	3.29 ± 0.96	0.93 (0.50–1.37)	0.0008
(% predicted)	(100.0 ± 20.1)	(108.0 ± 19.7)	8.0 (1.4–14.6)	0.023
FEV1/VC [%]	92.5 ± 6.3	89.5 ± 5.4	−3.0 (−8.0–1.9)	0.2
TLC [l]	3.39 ± 0.92	4.59 ± 1.32	1.21 (0.67–1.74)	0.0005
(% predicted)	(107.5 ± 14.5)	(110.2 ± 16.8)	2.77 (−7.21–12.7)	0.55
TLC – He [l]	3.53 ± 0.76	4.52 ± 1.22	0.98 (0.41–1.56)	0.003
(% predicted)	(114.1 ± 18.9)	(108.7 ± 14.8)	−5.48 (−21.6–10.6)	0.47
TGV [l]	1.93 ± 0.56	2.47 ± 0.93	0.53 (0.12–0.95)	0.017
(% predicted)	(117.4 ± 26.6)	(111.3 ± 30.2)	−6.0 (−27.9–15.8)	0.55
FRC – He [l]	1.83 ± 0.45	2.38 ± 0.81	0.55 (0.06–1.05)	0.03
(% predicted)	(119.0 ± 29.4)	(114.2 ± 22.4)	−4.86 (−31.0–21.3)	0.69
RV [l]	0.99 ± 0.34	1.28 ± 0.53	0.28 (0.01–0.56)	0.046
(% predicted)	(152.5 ± 65.5)	(142.0 ± 44.8)	−10.5 (−30.2–51.3)	0.58
RV – He [l]	1.27 ± 0.38	1.30 ± 0.38	0.03 (−0.30–0.37)	0.82
(% predicted)	(201.8 ± 103.6)	(146.7 ± 30.0)	−55.1 (−124.2–14.0)	0.11
DLCO [mmol/min/kPa]	5.82 ± 1.24	7.35 ± 1.82	1.53 (0.57–2.49)	0.005
(% predicted)	(79.3 ± 10.1)	(81.6 ± 14.7)	2.36 (−7.99–12.70)	0.62
VA [l]	3.39 ± 0.80	4.41 ± 1.20	1.02 (0.49–1.54)	0.001
(% predicted)	(97.4 ± 11.3)	(97.2 ± 14.0)	−0.3 (−11.3–10.7)	0.96

DLCO diffusing capacity for CO, corrected for blood hemoglobin concentration, *FEV1* forced expiratory volume in 1 s, *FRC* functional residual capacity (Helium dilution method), *FVC* forced vital capacity, *RV* residual volume (bodyplethysmography), *RV-He* residual volume (Helium dilution method), *TGV* thoracic gas volume at FRC (bodyplethysmography), *TLC* total lung capacity (bodyplethysmography), *TLC-He* total lung capacity (Helium dilution method), *VA* alveolar volume, *VC* vital capacity

values was observed [3]. Our normal initial results of PFTs are in accordance with these findings as we started measurements after clinical recovery and were looking for plausible long-term effects. One of the weaknesses of our study is the lack of PFTs measurement at the acute phase of the disease; hence, we did not determined whether there was any impairment in DLCO before V1 in our patients. Moreover, the clinical presentation was not homogenous, i.e., only 7 out of 11 subjects presented with hematuria and were treated with systemic steroids at the last HSP episode before V1. When the change in PFTs was assessed in this subgroup of patients, likewise, no differences between V1 and V2 were observed (data not shown).

An overt alveolar hemorrhage syndrome in the course of HSP is rare and often fatal, so the follow-up data is scarce. Although it is conceivable that in some cases it may lead to permanent pulmonary injury, in some published case reports, authors have suggested an overlap syndrome with other vasculitides such as microscopic polyangitis as a possible cause of this fatal complication rather than a rare presentation of HSP [8].

DLCO is sensitive to reveal alveolar barrier dysfunction. Nevertheless, it may not be sensitive enough to show minute changes that may have an impact on pulmonary function in the long-time range. Another approach to diagnose vascular-alveolar injury is a high resolution CT scan. Interestingly, probably due to ethical issues, there was no need to subject the pediatric population with no apparent pulmonary involvement to extensive radiation. Therefore, no reports on this diagnostic modality in HSP pediatric patients exist in databases.

Our study is just another one reporting no long-term sequelae of HSP on pulmonary function. Nevertheless, a longer follow-up and a larger group of HSP patients are needed to definitively address this issue.

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Compliance with ethical standards

Disclosures None.

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